

10/563073

## SEQUENCE LISTING

IAP20 Rec'd PCT/PTO 29 DEC 2005

<110> DOI, Hirofumi  
SAITO, Ken

<120> Method of treating diabetes by inhibiting degradation of at least one of CREBL1, ATF6, and HNF-4 alpha by HtrA

<130> 3190-089

<140> US Unassigned

<141> 2005-12-30

<150> PCT/JP2004/014377

<151> 2004-09-30

<150> JP P2003-342587

<151> 2003-09-30

<160> 35

<170> PatentIn version 3.1

<210> 1

<211> 1377

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<223> DNA that codes for HtrA2 precursor protein

<400> 1

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tcaggaactt ctgacccccg ggcccagagt acttatggga ccccagttct ctggggcccg	180
ttgtctgttg gggtcactga accccgagca tgcttgacgt ctgggacccc gggcccccg	240
gcacaactga ctgcggtgac ccagataacc aggaccggg aggcctcaga gaactctgga	300
accggttcgc gcgcgtggct ggcggtggcg ctgggcgctg ggggggcagt gctgttggtg	360
ttgtggggcg ggggtcgggg tcctccggcc gtctcgccg ccgtccctag ccgcccgc	420
gcttctcccc ggagtcagta caacttcac gcagatgtgg tggagaagac agcacctgcc	480
gtggtctata tcgagatcct ggaccggcac cctttcttgg gccgcgaggt ccctatctcg	540
aacggctcag gattcgtggt ggctgccgat gggctcattg tcaccaacgc ccatgtggtg	600
gctgatcggc gcagagtcgg tgtgagactg ctaagcggcg acacgtatga ggccgtggtc	660
acagctgtgg atcccgtggc agacatcgca acgctgagga ttcagactaa ggagcctctc	720
cccacgctgc ctctgggacg ctgagctgat gtccggcaag gggagtttgt tgttgccatg	780
ggaagtcctt ttgactgca gaacacgac acatccggca ttgttagctc tgctcagcgt	840
ccagccagag acctgggaact cccccaacc aatgtggaat acattcaaac tgatgcagct	900

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attgattttg gaaactctgg aggtccoctg gttaacctgg atggggaggt gattggagtg      960
aacaccatga aggtcacagc tggaatctcc ttgccatcc cttctgatcg tcttcgagag      1020
tttctgcata gtggggaaaa gaagaattcc tcctccggaa tcagtgggtc ccagcggcgc      1080
tacattgggg tgatgatgct gaccctgagt ccagcatcc ttgctgaact acagcttcga      1140
gaaccaagct ttcccgatgt tcagcatggt gtactcatcc ataaagtcac cctgggctcc      1200
cctgcacacc gggctggtct gcggcctggt gatgtgattt tggccattgg ggagcagatg      1260
gtacaaaatg ctgaagatgt ttatgaagct gttcgaaccc aatcccagtt ggcagtgcag      1320
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<210> 2
<211> 458
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> HtrA2 precursor protein

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<400> 2

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Met Ala Ala Pro Arg Ala Gly Arg Gly Ala Gly Trp Ser Leu Arg Ala
1           5           10           15

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Trp Arg Ala Leu Gly Gly Ile Arg Trp Gly Arg Arg Pro Arg Leu Thr
          20           25           30

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Pro Asp Leu Arg Ala Leu Leu Thr Ser Gly Thr Ser Asp Pro Arg Ala
          35           40           45

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Arg Val Thr Tyr Gly Thr Pro Ser Leu Trp Ala Arg Leu Ser Val Gly
          50           55           60

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Val Thr Glu Pro Arg Ala Cys Leu Thr Ser Gly Thr Pro Gly Pro Arg
65           70           75           80

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Ala Gln Leu Thr Ala Val Thr Pro Asp Thr Arg Thr Arg Glu Ala Ser
          85           90           95

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Glu Asn Ser Gly Thr Arg Ser Arg Ala Trp Leu Ala Val Ala Leu Gly
          100          105          110

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Ala Gly Gly Ala Val Leu Leu Leu Leu Trp Gly Gly Gly Arg Gly Pro
          115          120          125

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Pro Ala Val Leu Ala Ala Val Pro Ser Pro Pro Pro Ala Ser Pro Arg

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130	135	140
Ser Gln Tyr Asn Phe Ile Ala Asp Val Val Glu Lys Thr Ala Pro Ala 145 150 155 160		
Val Val Tyr Ile Glu Ile Leu Asp Arg His Pro Phe Leu Gly Arg Glu 165 170 175		
Val Pro Ile Ser Asn Gly Ser Gly Phe Val Val Ala Ala Asp Gly Leu 180 185 190		
Ile Val Thr Asn Ala His Val Val Ala Asp Arg Arg Arg Val Arg Val 195 200 205		
Arg Leu Leu Ser Gly Asp Thr Tyr Glu Ala Val Val Thr Ala Val Asp 210 215 220		
Pro Val Ala Asp Ile Ala Thr Leu Arg Ile Gln Thr Lys Glu Pro Leu 225 230 235 240		
Pro Thr Leu Pro Leu Gly Arg Ser Ala Asp Val Arg Gln Gly Glu Phe 245 250 255		
Val Val Ala Met Gly Ser Pro Phe Ala Leu Gln Asn Thr Ile Thr Ser 260 265 270		
Gly Ile Val Ser Ser Ala Gln Arg Pro Ala Arg Asp Leu Gly Leu Pro 275 280 285		
Gln Thr Asn Val Glu Tyr Ile Gln Thr Asp Ala Ala Ile Asp Phe Gly 290 295 300		
Asn Ser Gly Gly Pro Leu Val Asn Leu Asp Gly Glu Val Ile Gly Val 305 310 315 320		
Asn Thr Met Lys Val Thr Ala Gly Ile Ser Phe Ala Ile Pro Ser Asp 325 330 335		
Arg Leu Arg Glu Phe Leu His Arg Gly Glu Lys Lys Asn Ser Ser Ser 340 345 350		
Gly Ile Ser Gly Ser Gln Arg Arg Tyr Ile Gly Val Met Met Leu Thr 355 360 365		
Leu Ser Pro Ser Ile Leu Ala Glu Leu Gln Leu Arg Glu Pro Ser Phe 370 375 380		

Pro Asp Val Gln His Gly Val Leu Ile His Lys Val Ile Leu Gly Ser  
 385 390 395 400

Pro Ala His Arg Ala Gly Leu Arg Pro Gly Asp Val Ile Leu Ala Ile  
 405 410 415

Gly Glu Gln Met Val Gln Asn Ala Glu Asp Val Tyr Glu Ala Val Arg  
 420 425 430

Thr Gln Ser Gln Leu Ala Val Gln Ile Arg Arg Gly Arg Glu Thr Leu  
 435 440 445

Thr Leu Tyr Val Thr Pro Glu Val Thr Glu  
 450 455

<210> 3  
 <211> 981  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> DNA that codes for mature HtrA2

<400> 3  
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 gtggtggaga agacagcacc tgccgtggtc tatatcgaga tcctggaccg gcaccctttc 120  
 ttgggccgag aggtccctat ctggaacggc tcaggattcg tgggtggctgc cgatgggctc 180  
 attgtcacca acgcccattg ggtggctgat cggcgagag tccgtgtgag actgctaagc 240  
 ggcgacacgt atgaggccgt ggtcacagct gtggatcccg tggcagacat cgcaacgctg 300  
 aggattcaga ctaaggagcc tctccccacg ctgcctctgg gacgctcagc tgatgtccgg 360  
 caaggggagt ttgttgttgc catgggaagt ccttttgac tgcagaacac gatcacatcc 420  
 ggcattgtta gctctgtca gcgtccagcc agagacctgg gactcccca aaccaatgtg 480  
 gaatacattc aaactgatgc agctattgat tttggaaact ctggaggtcc cctggttaac 540  
 ctggatgggg aggtgattgg agtgaacacc atgaaggatc cagctggaat ctcctttgcc 600  
 atcccttctg atcgtcttcg agagtttctg catcgtgggg aaaagaagaa ttctctctcc 660  
 ggaatcagtg ggtcccagcg gcgctacatt ggggtgatga tgctgaccct gagtcccagc 720  
 atccttgctg aactacagct tcgagaacca agctttcccg atgttcagca tgggtgtactc 780  
 atccataaag tcacctctgg ctcccctgca caccgggctg gtctgcggcc tggatgatgtg 840  
 attttggcca ttggggagca gatggtacaa aatgctgaag atgtttatga agctgttcga 900  
 acccaatccc agttggcagt gcagatccgg cggggacgag aaacactgac cttatatgtg 960

<210> 4  
<211> 326  
<212> PRT  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<223> mature HtrA2

<400> 4

Met Ala Val Pro Ser Pro Pro Pro Ala Ser Pro Arg Ser Gln Tyr Asn  
1 5 10 15

Phe Ile Ala Asp Val Val Glu Lys Thr Ala Pro Ala Val Val Tyr Ile  
20 25 30

Glu Ile Leu Asp Arg His Pro Phe Leu Gly Arg Glu Val Pro Ile Ser  
35 40 45

Asn Gly Ser Gly Phe Val Val Ala Ala Asp Gly Leu Ile Val Thr Asn  
50 55 60

Ala His Val Val Ala Asp Arg Arg Arg Val Arg Val Arg Leu Leu Ser  
65 70 75 80

Gly Asp Thr Tyr Glu Ala Val Val Thr Ala Val Asp Pro Val Ala Asp  
85 90 95

Ile Ala Thr Leu Arg Ile Gln Thr Lys Glu Pro Leu Pro Thr Leu Pro  
100 105 110

Leu Gly Arg Ser Ala Asp Val Arg Gln Gly Glu Phe Val Val Ala Met  
115 120 125

Gly Ser Pro Phe Ala Leu Gln Asn Thr Ile Thr Ser Gly Ile Val Ser  
130 135 140

Ser Ala Gln Arg Pro Ala Arg Asp Leu Gly Leu Pro Gln Thr Asn Val  
145 150 155 160

Glu Tyr Ile Gln Thr Asp Ala Ala Ile Asp Phe Gly Asn Ser Gly Gly  
165 170 175

Pro Leu Val Asn Leu Asp Gly Glu Val Ile Gly Val Asn Thr Met Lys  
180 185 190

Val Thr Ala Gly Ile Ser Phe Ala Ile Pro Ser Asp Arg Leu Arg Glu  
195 200 205

Phe Leu His Arg Gly Glu Lys Lys Asn Ser Ser Ser Gly Ile Ser Gly  
210 215 220

Ser Gln Arg Arg Tyr Ile Gly Val Met Met Leu Thr Leu Ser Pro Ser  
225 230 235 240

Ile Leu Ala Glu Leu Gln Leu Arg Glu Pro Ser Phe Pro Asp Val Gln  
245 250 255

His Gly Val Leu Ile His Lys Val Ile Leu Gly Ser Pro Ala His Arg  
260 265 270

Ala Gly Leu Arg Pro Gly Asp Val Ile Leu Ala Ile Gly Glu Gln Met  
275 280 285

Val Gln Asn Ala Glu Asp Val Tyr Glu Ala Val Arg Thr Gln Ser Gln  
290 295 300

Leu Ala Val Gln Ile Arg Arg Gly Arg Glu Thr Leu Thr Leu Tyr Val  
305 310 315 320

Thr Pro Glu Val Thr Glu  
325

<210> 5  
<211> 981  
<212> DNA  
<213> Artificial

<220>  
<223> Polynucleotide consisting of the same base sequence of SEQ ID NO:  
3 wherein the nucleotide of position 520 is g

<220>  
<221> misc\_feature  
<223> DNA that codes for mature HtrA2 (S306A)

<400> 5  
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ttggggccgc aggtccctat ctcgaacggc tcaggattcg tgggtggctgc cgatgggctc 180  
attgtcacca acgcccattg ggtggctgat cggcgagag tccgtgtgag actgctaagc 240  
ggcgacacgt atgaggccgt ggtcacagct gtggatcccg tggcagacat cgcaacgctg 300  
aggattcaga ctaaggagcc tctccccacg ctgcctctgg gacgctcagc tgatgtccgg 360

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caaggggagt ttgttgttgc catgggaagt ccctttgcac tgcagaacac gatcacatcc 420
ggcattgtta gctctgctca gcgtccagcc agagacctgg gactccccca aaccaatgtg 480
gaatacattc aaactgatgc agctattgat tttggaaacg ctggagggtcc cctgggtaac 540
ctggatgggg aggtgattgg agtgaacacc atgaagggtca cagctggaat ctcctttgcc 600
atcccttctg atcgtcttcg agagtttctg catcgtgggg aaaagaagaa ttcctcctcc 660
ggaatcagtg ggtcccagcg gcgctacatt ggggtgatga tgctgaccct gagtcccagc 720
atccttgctg aactacagct tcgagaacca agctttcccg atgttcagca tgggtgtactc 780
atccataaag tcatcctggg ctcccctgca caccgggctg gtctgcggcc tgggtgatgtg 840
atcttgacca ttggggagca gatggtacaa aatgctgaag atgtttatga agctgttcga 900
acccaatccc agttggcagt gcagatccgg cggggacgag aaacactgac cttatatgtg 960
accctgagg tcacagaatg a 981

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<210> 6
<211> 326
<212> PRT
<213> Artificial

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<220>
<223> Polypeptide consisting of the same amino acid sequence of SEQ ID
      NO:4 wherein the 174th amino acid residue is substituted by Ala

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<220>
<221> misc_feature
<223> mature HtrA2(S306A)

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<400> 6

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Met Ala Val Pro Ser Pro Pro Pro Ala Ser Pro Arg Ser Gln Tyr Asn
1           5           10           15

```

```

Phe Ile Ala Asp Val Val Glu Lys Thr Ala Pro Ala Val Val Tyr Ile
          20           25           30

```

```

Glu Ile Leu Asp Arg His Pro Phe Leu Gly Arg Glu Val Pro Ile Ser
          35           40           45

```

```

Asn Gly Ser Gly Phe Val Val Ala Ala Asp Gly Leu Ile Val Thr Asn
          50           55           60

```

```

Ala His Val Val Ala Asp Arg Arg Arg Val Arg Val Arg Leu Leu Ser
          65           70           75           80

```

```

Gly Asp Thr Tyr Glu Ala Val Val Thr Ala Val Asp Pro Val Ala Asp
          85           90           95

```

Ile	Ala	Thr	Leu	Arg	Ile	Gln	Thr	Lys	Glu	Pro	Leu	Pro	Thr	Leu	Pro		
			100					105					110				
Leu	Gly	Arg	Ser	Ala	Asp	Val	Arg	Gln	Gly	Glu	Phe	Val	Val	Ala	Met		
		115					120					125					
Gly	Ser	Pro	Phe	Ala	Leu	Gln	Asn	Thr	Ile	Thr	Ser	Gly	Ile	Val	Ser		
	130					135					140						
Ser	Ala	Gln	Arg	Pro	Ala	Arg	Asp	Leu	Gly	Leu	Pro	Gln	Thr	Asn	Val		
145					150					155					160		
Glu	Tyr	Ile	Gln	Thr	Asp	Ala	Ala	Ile	Asp	Phe	Gly	Asn	Ala	Gly	Gly		
				165					170					175			
Pro	Leu	Val	Asn	Leu	Asp	Gly	Glu	Val	Ile	Gly	Val	Asn	Thr	Met	Lys		
			180					185					190				
Val	Thr	Ala	Gly	Ile	Ser	Phe	Ala	Ile	Pro	Ser	Asp	Arg	Leu	Arg	Glu		
		195					200					205					
Phe	Leu	His	Arg	Gly	Glu	Lys	Lys	Asn	Ser	Ser	Ser	Gly	Ile	Ser	Gly		
	210					215					220						
Ser	Gln	Arg	Arg	Tyr	Ile	Gly	Val	Met	Met	Leu	Thr	Leu	Ser	Pro	Ser		
225					230					235					240		
Ile	Leu	Ala	Glu	Leu	Gln	Leu	Arg	Glu	Pro	Ser	Phe	Pro	Asp	Val	Gln		
				245					250					255			
His	Gly	Val	Leu	Ile	His	Lys	Val	Ile	Leu	Gly	Ser	Pro	Ala	His	Arg		
			260					265					270				
Ala	Gly	Leu	Arg	Pro	Gly	Asp	Val	Ile	Leu	Ala	Ile	Gly	Glu	Gln	Met		
		275					280					285					
Val	Gln	Asn	Ala	Glu	Asp	Val	Tyr	Glu	Ala	Val	Arg	Thr	Gln	Ser	Gln		
		290				295					300						
Leu	Ala	Val	Gln	Ile	Arg	Arg	Gly	Arg	Glu	Thr	Leu	Thr	Leu	Tyr	Val		
305					310					315					320		
Thr	Pro	Glu	Val	Thr	Glu												
				325													

<210> 7  
 <211> 969  
 <212> DNA



<213> Artificial

<220>

<223> Polynucleotide consisting of the same base sequence of SEQ ID NO: 3 wherein the nucleotides of position 4-15 are deleted

<220>

<221> misc\_feature

<223> DNA that codes for mature HtrA2(delta AVPS)

<400> 7

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acagcacctg ccgtggtcta tatcgagatc ctggaccggc accctttctt gggccgcgag      120
gtccctatct cgaacggctc aggattcgtg gtggctgccg atggggtcat tgtcaccaac      180
gcccatgtgg tggctgatcg gcgcagagtc cgtgtgagac tgctaagcgg cgacacgtat      240
gaggccgtgg tcacagctgt ggatcccgtg gcagacatcg caacgctgag gattcagact      300
aaggagcctc tccccacgct gcctctggga cgctcagctg atgtccggca aggggagttt      360
gttgttgcc a tgggaagtcc ctttgactg cagaacacga tcacatccgg cattgttagc      420
tctgctcagc gtccagccag agacctggga ctccccaaaa ccaatgtgga atacattcaa      480
actgatgcag ctattgattt tggaaactct ggaggtcccc tggttaacct ggatggggag      540
gtgattggag tgaacaccat gaaggtcaca gctggaatct cctttgccat cccttctgat      600
cgtcttcgag agtttctgca tcgtggggaa aagaagaatt cctcctccgg aatcagtggg      660
tcccagcggc gctacattgg ggtgatgatg ctgaccctga gtcccagcat ccttgctgaa      720
ctacagcttc gagaaccaag ctttcccgat gttcagcatg gtgtactcat ccataaagtc      780
atcctgggct cccctgcaca ccgggctggg ctgcggcctg gtgatgtgat tttggccatt      840
ggggagcaga tggtaaaaa tgctgaagat gtttatgaag ctgttcgaac ccaatccag      900
ttggcagtgc agatccggcg gggacgagaa aactgacct tatatgtgac ccctgaggtc      960
acagaatga                                     969
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<210> 8

<211> 322

<212> PRT

<213> Artificial

<220>

<223> Polypeptide consisting of the same amino acid sequence of SEQ ID NO:4 wherein the amino acid residues from the 2nd to the 5th are deleted

<220>

<221> misc\_feature

<223> mature HtrA2(delta AVPS)

<400> 8

Met	Pro	Pro	Pro	Ala	Ser	Pro	Arg	Ser	Gln	Tyr	Asn	Phe	Ile	Ala	Asp	1	5	10	15
Val	Val	Glu	Lys	Thr	Ala	Pro	Ala	Val	Val	Tyr	Ile	Glu	Ile	Leu	Asp	20	25	30	
Arg	His	Pro	Phe	Leu	Gly	Arg	Glu	Val	Pro	Ile	Ser	Asn	Gly	Ser	Gly	35	40	45	
Phe	Val	Val	Ala	Ala	Asp	Gly	Leu	Ile	Val	Thr	Asn	Ala	His	Val	Val	50	55	60	
Ala	Asp	Arg	Arg	Arg	Val	Arg	Val	Arg	Leu	Leu	Ser	Gly	Asp	Thr	Tyr	65	70	75	80
Glu	Ala	Val	Val	Thr	Ala	Val	Asp	Pro	Val	Ala	Asp	Ile	Ala	Thr	Leu	85	90	95	
Arg	Ile	Gln	Thr	Lys	Glu	Pro	Leu	Pro	Thr	Leu	Pro	Leu	Gly	Arg	Ser	100	105	110	
Ala	Asp	Val	Arg	Gln	Gly	Glu	Phe	Val	Val	Ala	Met	Gly	Ser	Pro	Phe	115	120	125	
Ala	Leu	Gln	Asn	Thr	Ile	Thr	Ser	Gly	Ile	Val	Ser	Ser	Ala	Gln	Arg	130	135	140	
Pro	Ala	Arg	Asp	Leu	Gly	Leu	Pro	Gln	Thr	Asn	Val	Glu	Tyr	Ile	Gln	145	150	155	160
Thr	Asp	Ala	Ala	Ile	Asp	Phe	Gly	Asn	Ser	Gly	Gly	Pro	Leu	Val	Asn	165	170	175	
Leu	Asp	Gly	Glu	Val	Ile	Gly	Val	Asn	Thr	Met	Lys	Val	Thr	Ala	Gly	180	185	190	
Ile	Ser	Phe	Ala	Ile	Pro	Ser	Asp	Arg	Leu	Arg	Glu	Phe	Leu	His	Arg	195	200	205	
Gly	Glu	Lys	Lys	Asn	Ser	Ser	Ser	Gly	Ile	Ser	Gly	Ser	Gln	Arg	Arg	210	215	220	
Tyr	Ile	Gly	Val	Met	Met	Leu	Thr	Leu	Ser	Pro	Ser	Ile	Leu	Ala	Glu	225	230	235	240
Leu	Gln	Leu	Arg	Glu	Pro	Ser	Phe	Pro	Asp	Val	Gln	His	Gly	Val	Leu	245	250	255	

Ile His Lys Val Ile Leu Gly Ser Pro Ala His Arg Ala Gly Leu Arg  
260 265 270

Pro Gly Asp Val Ile Leu Ala Ile Gly Glu Gln Met Val Gln Asn Ala  
275 280 285

Glu Asp Val Tyr Glu Ala Val Arg Thr Gln Ser Gln Leu Ala Val Gln  
290 295 300

Ile Arg Arg Gly Arg Glu Thr Leu Thr Leu Tyr Val Thr Pro Glu Val  
305 310 315 320

Thr Glu

<210> 9  
<211> 981  
<212> DNA  
<213> Artificial

<220>  
<223> Polynucleotide consisting of the same base sequence of SEQ ID NO:  
3 wherein the nucleotide of position 5 is g

<220>  
<221> misc\_feature  
<223> DNA that codes for mature HtrA2 (GVPS)

<400> 9  
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ttgggccgcg aggtccctat ctgcaacggc tcaggattcg tgggtggctgc cgatgggctc 180  
attgtcacca acgcccattg ggtggctgat cggcgagag tccgtgtgag actgctaagc 240  
ggcgacacgt atgaggccgt ggtcacagct gtggatcccg tggcagacat cgcaacgctg 300  
aggattcaga ctaaggagcc tctccccacg ctgcctctgg gacgctcagc tgatgtccgg 360  
caaggggagt ttgttgttgc catgggaagt ccctttgcac tgcagaacac gatcacatcc 420  
ggcattgtta gctctgctca gcgtccagcc agagacctgg gactccccca aaccaatgtg 480  
gaatacattc aaactgatgc agctattgat tttggaaact ctggaggtcc cctggttaac 540  
ctggatgggg aggtgattgg agtgaacacc atgaaggatc cagctggaat ctcctttgcc 600  
atcccttctg atcgtcttcg agagtttctg catcgtgggg aaaagaagaa ttcctcctcc 660  
ggaatcagtg ggtcccagcg gcgctacatt ggggtgatga tgctgaccct gagtcccagc 720  
atccttgctg aactacagct tcgagaacca agctttcccg atgttcagca tgggtgactc 780

atccataaag tcatcctggg ctcccctgca caccgggctg gtctgcggcc tggatgatgtg 840  
 attttggcca ttggggagca gatggta~~caa~~ aatgctgaag atgtttatga agctgttcga 900  
 acccaatccc agttggcagt gcagatccgg cggggacgag aaacactgac cttatatgtg 960  
 acccctgagg tcacagaatg a 981

<210> 10  
 <211> 326  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Polypeptide consisting of the same amino acid sequence of SEQ ID NO:4 wherein the 2nd amino acid residue is substituted by Gly

<220>  
 <221> misc\_feature  
 <223> mature HtrA2 (GVPS)

<400> 10

Met Gly Val Pro Ser Pro Pro Pro Ala Ser Pro Arg Ser Gln Tyr Asn  
 1 5 10 15

Phe Ile Ala Asp Val Val Glu Lys Thr Ala Pro Ala Val Val Tyr Ile  
 20 25 30

Glu Ile Leu Asp Arg His Pro Phe Leu Gly Arg Glu Val Pro Ile Ser  
 35 40 45

Asn Gly Ser Gly Phe Val Val Ala Ala Asp Gly Leu Ile Val Thr Asn  
 50 55 60

Ala His Val Val Ala Asp Arg Arg Arg Val Arg Val Arg Leu Leu Ser  
 65 70 75 80

Gly Asp Thr Tyr Glu Ala Val Val Thr Ala Val Asp Pro Val Ala Asp  
 85 90 95

Ile Ala Thr Leu Arg Ile Gln Thr Lys Glu Pro Leu Pro Thr Leu Pro  
 100 105 110

Leu Gly Arg Ser Ala Asp Val Arg Gln Gly Glu Phe Val Val Ala Met  
 115 120 125

Gly Ser Pro Phe Ala Leu Gln Asn Thr Ile Thr Ser Gly Ile Val Ser  
 130 135 140

Ser Ala Gln Arg Pro Ala Arg Asp Leu Gly Leu Pro Gln Thr Asn Val  
 145 150 155 160

Glu Tyr Ile Gln Thr Asp Ala Ala Ile Asp Phe Gly Asn Ser Gly Gly  
 165 170 175

Pro Leu Val Asn Leu Asp Gly Glu Val Ile Gly Val Asn Thr Met Lys  
 180 185 190

Val Thr Ala Gly Ile Ser Phe Ala Ile Pro Ser Asp Arg Leu Arg Glu  
 195 200 205

Phe Leu His Arg Gly Glu Lys Lys Asn Ser Ser Ser Gly Ile Ser Gly  
 210 215 220

Ser Gln Arg Arg Tyr Ile Gly Val Met Met Leu Thr Leu Ser Pro Ser  
 225 230 235 240

Ile Leu Ala Glu Leu Gln Leu Arg Glu Pro Ser Phe Pro Asp Val Gln  
 245 250 255

His Gly Val Leu Ile His Lys Val Ile Leu Gly Ser Pro Ala His Arg  
 260 265 270

Ala Gly Leu Arg Pro Gly Asp Val Ile Leu Ala Ile Gly Glu Gln Met  
 275 280 285

Val Gln Asn Ala Glu Asp Val Tyr Glu Ala Val Arg Thr Gln Ser Gln  
 290 295 300

Leu Ala Val Gln Ile Arg Arg Gly Arg Glu Thr Leu Thr Leu Tyr Val  
 305 310 315 320

Thr Pro Glu Val Thr Glu  
 325

<210> 11  
 <211> 969  
 <212> DNA  
 <213> Artificial

<220>  
 <223> Polynucleotide consisting of the same base sequence of SEQ ID NO:  
 5 wherein the nucleotides of position 4-15 are deleted

<220>  
 <221> misc\_feature  
 <223> DNA that codes for mature HtrA2(S306A, delta AVPS)

<400> 11  
 atgcccgc cgccttctcc ccggagtcag tacaacttca tcgcagatgt ggtggagaag 60

```

acagcacctg ccgtggtcta tatcgagatc ctggaccggc accctttctt gggccgcgag      120
gtccctatct cgaacggctc aggatttctg gtggctgccg atgggctcat tgtcaccaac      180
gcccattgtg tggctgatcg gcgcagagtc cgtgtgagac tgctaagcgg cgacacgtat      240
gaggccgtgg tcacagctgt ggatcccgtg gcagacatcg caacgctgag gattcagact      300
aaggagcctc tccccacgct gcctctggga cgctcagctg atgtccggca aggggagttt      360
gttggttgcca tgggaagtcc ctttgactg  cagaacacga tcacatccgg cattgttagc      420
tctgctcagc gtccagccag agacctggga ctccccaaa ccaatgtgga atacattcaa      480
actgatgcag ctattgattt tggaaacgct ggagggtccc tggttaacct ggatggggag      540
gtgattggag tgaacaccat gaaggtcaca gctggaatct ctttgccat cccttctgat      600
cgtcttcgag agtttctgca tcgtggggaa aagaagaatt cctcctccgg aatcagtggg      660
tcccagcggc gctacattgg ggtgatgatg ctgaccctga gtcccagcat ctttgctgaa      720
ctacagcttc gagaaccaag ctttcccgat gttcagcatg gtgtactcat ccataaagtc      780
atcctgggct cccctgcaca ccgggctggg ctgcccctg  gtgatgtgat tttggccatt      840
ggggagcaga tggtaaaaa tgctgaagat gtttatgaag ctgttcgaac ccaatcccag      900
ttggcagtgc agatccggcg gggacgagaa aactgacct tatatgtgac ccctgaggtc      960
acagaatga                                                                969

```

```

<210> 12
<211> 322
<212> PRT
<213> Artificial

```

```

<220>
<223> Polypeptide consisting of the same amino acid sequence of SEQ ID
      NO:6 wherein the amino acid residues from the 2nd to the 5th are
      deleted

```

```

<220>
<221> misc_feature
<223> mature HtrA2(S306A, delta AVPS)

```

```

<400> 12

```

```

Met Pro Pro Pro Ala Ser Pro Arg Ser Gln Tyr Asn Phe Ile Ala Asp
1           5           10          15

```

```

Val Val Glu Lys Thr Ala Pro Ala Val Val Tyr Ile Glu Ile Leu Asp
          20          25          30

```

```

Arg His Pro Phe Leu Gly Arg Glu Val Pro Ile Ser Asn Gly Ser Gly
          35          40          45

```

```

Phe Val Val Ala Ala Asp Gly Leu Ile Val Thr Asn Ala His Val Val

```

50					55					60					
Ala	Asp	Arg	Arg	Arg	Val	Arg	Val	Arg	Leu	Leu	Ser	Gly	Asp	Thr	Tyr
65					70					75					80
Glu	Ala	Val	Val	Thr	Ala	Val	Asp	Pro	Val	Ala	Asp	Ile	Ala	Thr	Leu
				85					90					95	
Arg	Ile	Gln	Thr	Lys	Glu	Pro	Leu	Pro	Thr	Leu	Pro	Leu	Gly	Arg	Ser
			100					105					110		
Ala	Asp	Val	Arg	Gln	Gly	Glu	Phe	Val	Val	Ala	Met	Gly	Ser	Pro	Phe
		115					120					125			
Ala	Leu	Gln	Asn	Thr	Ile	Thr	Ser	Gly	Ile	Val	Ser	Ser	Ala	Gln	Arg
	130					135						140			
Pro	Ala	Arg	Asp	Leu	Gly	Leu	Pro	Gln	Thr	Asn	Val	Glu	Tyr	Ile	Gln
145					150					155					160
Thr	Asp	Ala	Ala	Ile	Asp	Phe	Gly	Asn	Ala	Gly	Gly	Pro	Leu	Val	Asn
				165					170					175	
Leu	Asp	Gly	Glu	Val	Ile	Gly	Val	Asn	Thr	Met	Lys	Val	Thr	Ala	Gly
			180					185					190		
Ile	Ser	Phe	Ala	Ile	Pro	Ser	Asp	Arg	Leu	Arg	Glu	Phe	Leu	His	Arg
		195					200					205			
Gly	Glu	Lys	Lys	Asn	Ser	Ser	Ser	Gly	Ile	Ser	Gly	Ser	Gln	Arg	Arg
	210					215					220				
Tyr	Ile	Gly	Val	Met	Met	Leu	Thr	Leu	Ser	Pro	Ser	Ile	Leu	Ala	Glu
225					230					235					240
Leu	Gln	Leu	Arg	Glu	Pro	Ser	Phe	Pro	Asp	Val	Gln	His	Gly	Val	Leu
				245					250					255	
Ile	His	Lys	Val	Ile	Leu	Gly	Ser	Pro	Ala	His	Arg	Ala	Gly	Leu	Arg
			260					265					270		
Pro	Gly	Asp	Val	Ile	Leu	Ala	Ile	Gly	Glu	Gln	Met	Val	Gln	Asn	Ala
		275					280					285			
Glu	Asp	Val	Tyr	Glu	Ala	Val	Arg	Thr	Gln	Ser	Gln	Leu	Ala	Val	Gln
	290					295					300				

Ile Arg Arg Gly Arg Glu Thr Leu Thr Leu Tyr Val Thr Pro Glu Val  
 305 310 315 320

Thr Glu

<210> 13  
 <211> 981  
 <212> DNA  
 <213> Artificial

<220>  
 <223> Polynucleotide consisting of the same base sequence of SEQ ID NO:  
 5 wherein the nucleotide of position 5 is g

<220>  
 <221> misc\_feature  
 <223> DNA that codes for mature HtrA2(S306A, GVPS)

<400> 13  
 atggggtgcc ctagcccgcc gcccgcttct ccccgaggtc agtacaactt catcgcatat 60  
 gtggtggaga agacagcacc tgccgtgggc tatatcgaga tcctggaccg gcaccctttc 120  
 ttgggccgag aggtccctat ctggaacggc tcaggattcg tgggtggtgc cgatgggctc 180  
 attgtcacca acgcccattg ggtggctgat cggcgcatag tccgtgtgag actgctaagc 240  
 ggcgacacgt atgaggccgt ggtcacagct gtggatcccg tggcagacat cgcaacgctg 300  
 aggattcaga ctaaggagcc tctccccacg ctgcctctgg gacgctcagc tgatgtccgg 360  
 caaggggagt ttgtttgttc catgggaagt ccctttgcac tgcagaacac gatcacatcc 420  
 ggcattgtta gctctgctca gcgtccagcc agagacctgg gactccccca aaccaatgtg 480  
 gaatacatcc aaactgatgc agctattgat tttggaaacg ctggaggtcc cctgggttaac 540  
 ctggatgggg aggtgattgg agtgaacacc atgaaggcca cagctggaat ctcccttgcc 600  
 atcccttctg atcgtcttcg agagtttctg catcgtgggg aaaagaagaa ttcctcctcc 660  
 ggaatcagtg ggtcccagcg gcgctacatt ggggtgatga tgctgaccct gagtcccagc 720  
 atccttgctg aactacagct tcgagaacca agctttcccg atgttcagca tgggtgtactc 780  
 atccataaag tcctcctggg ctcccctgca caccgggctg gtctgcggcc tgggtgatgtg 840  
 attttggcca ttggggagca gatggtacaa aatgctgaag atgtttatga agctgttcga 900  
 acccaatccc agttggcagt gcagatcccg cggggacgag aaacactgac cttatatgtg 960  
 acccctgagg tcacagaatg a 981

<210> 14  
 <211> 326  
 <212> PRT  
 <213> Artificial



<220>

<223> Polypeptide consisting of the same amino acid sequence of SEQ ID NO:6 wherein the 2nd amino acid residue is substituted by Gly

<220>

<221> misc\_feature

<223> mature HtrA2(S306A, GVPS)

<400> 14

Met Gly Val Pro Ser Pro Pro Pro Ala Ser Pro Arg Ser Gln Tyr Asn  
1 5 10 15

Phe Ile Ala Asp Val Val Glu Lys Thr Ala Pro Ala Val Val Tyr Ile  
20 25 30

Glu Ile Leu Asp Arg His Pro Phe Leu Gly Arg Glu Val Pro Ile Ser  
35 40 45

Asn Gly Ser Gly Phe Val Val Ala Ala Asp Gly Leu Ile Val Thr Asn  
50 55 60

Ala His Val Val Ala Asp Arg Arg Arg Val Arg Val Arg Leu Leu Ser  
65 70 75 80

Gly Asp Thr Tyr Glu Ala Val Val Thr Ala Val Asp Pro Val Ala Asp  
85 90 95

Ile Ala Thr Leu Arg Ile Gln Thr Lys Glu Pro Leu Pro Thr Leu Pro  
100 105 110

Leu Gly Arg Ser Ala Asp Val Arg Gln Gly Glu Phe Val Val Ala Met  
115 120 125

Gly Ser Pro Phe Ala Leu Gln Asn Thr Ile Thr Ser Gly Ile Val Ser  
130 135 140

Ser Ala Gln Arg Pro Ala Arg Asp Leu Gly Leu Pro Gln Thr Asn Val  
145 150 155 160

Glu Tyr Ile Gln Thr Asp Ala Ala Ile Asp Phe Gly Asn Ala Gly Gly  
165 170 175

Pro Leu Val Asn Leu Asp Gly Glu Val Ile Gly Val Asn Thr Met Lys  
180 185 190

Val Thr Ala Gly Ile Ser Phe Ala Ile Pro Ser Asp Arg Leu Arg Glu  
195 200 205

Phe Leu His Arg Gly Glu Lys Lys Asn Ser Ser Ser Gly Ile Ser Gly  
 210 215 220  
 Ser Gln Arg Arg Tyr Ile Gly Val Met Met Leu Thr Leu Ser Pro Ser  
 225 230 235 240  
 Ile Leu Ala Glu Leu Gln Leu Arg Glu Pro Ser Phe Pro Asp Val Gln  
 245 250 255  
 His Gly Val Leu Ile His Lys Val Ile Leu Gly Ser Pro Ala His Arg  
 260 265 270  
 Ala Gly Leu Arg Pro Gly Asp Val Ile Leu Ala Ile Gly Glu Gln Met  
 275 280 285  
 Val Gln Asn Ala Glu Asp Val Tyr Glu Ala Val Arg Thr Gln Ser Gln  
 290 295 300  
 Leu Ala Val Gln Ile Arg Arg Gly Arg Glu Thr Leu Thr Leu Tyr Val  
 305 310 315 320  
 Thr Pro Glu Val Thr Glu  
 325

<210> 15  
 <211> 2112  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> DNA that codes for CREBL1

<400> 15  
 atggcgaggc tgatgctgct cagcgagatt gctgaccgga cgcgtttctt caccgacaac 60  
 ctgcttagcc cggaggactg ggggtctgcag aacagcacct tgtattcttg cctagatgaa 120  
 gtggccgagg agcagacgca gctcttccgt tgcccgagc aggatgtccc gtttgacggc 180  
 agctccctgg acgtggggat ggatgtcagc ccctctgagc ccccatggga actcctgccg 240  
 atcttcccag atcttcaggt gaagtctgag ccattctccc cctgctcttc ctccctccctc 300  
 agctccgagt catcgctct ctccacagag ccattcagcg aggtctcttg ggtaggggag 360  
 gtgtccatg tgaagacaga gtccttggca ccccaactgt gtctcctggg agatgaccca 420  
 acatcctcat ttgaaaccgt ccagatcaat gttatcccca cctctgatga ttcctcagat 480  
 gtccagacca agatagaacc tgtctctcca tgttcttccg tcaactctga ggctccctg 540  
 ctctcagccg actcctccag ccaggctttt ataggagagg aggtcctgga agtgaagaca 600

gagtcctgt ccccttcagg atgcctcctg tgggatgtcc cagccccctc acttggagct	660
gtccagatca gcatggggcc atcccttgat ggctcctcag gcaaagccct gcccaaccgg	720
aagccgccac tgcagcccaa acctgtagtg ctaaccactg tcccaatgcc atccagagct	780
gtgcctccca gcaccaagct ccttctgcag tccctcgtcc agccaccccc agtgtcccca	840
gttgctctca tccagggtgc tattcgagtc cagcctgaag ggccgggtcc ctctctacca	900
cggcctgaga ggaagagcat cgttcccgtc cctatgcctg gaaactcctg cccgcctgaa	960
gtggatgcaa agctgctgaa gcggcagcag cgaatgatca agaaccggga gtcagcctgc	1020
cagtcocgga gaaagaagaa agagtatctg cagggactgg aggctcggct gcaagcagta	1080
ctggctgaca accagcagct ccgccgagag aatgctgccc tccggcggcg gctggaggcc	1140
ctgctggctg aaaacagcga gctcaagtta gggctctggaa acaggaaggt ggtctgcata	1200
atggtcttcc ttctcttcat tgccttcaac tttggacctg tcagcatcag tgagcctcct	1260
tcagctccca tctctcctcg gatgaacaag ggggagcctc aaccccgag acatttgctg	1320
gggttctcag agcaagagcc agttcaggga gttgaacctc tccaggggtc ctcccagggc	1380
cctaaggagc cccagcccag cccacagac cagcccagtt tcagcaacct gacagccttc	1440
cctgggggcg ccaaggagct actactaaga gacctagacc agctcttctc ctctctgat	1500
tgccggcact tcaaccgcac tgagtccctg aggttgctg acgagttgag tggctgggtc	1560
cagcgccacc agagaggccg gaggaagatc cctcagaggg cccaggagag acagaagtct	1620
cagccacgga agaagtcacc tccagttaag gcagtcccca tccaaccccc tggaccccca	1680
gaaagggatt ctgtgggcca gctgcaacta tatcgccacc cagaccgttc gcagccagca	1740
ttcttggatg caattgaccg acgggaagac acattttatg ttgtctcttt ccgaagggac	1800
cacctgctgc tcccagccat cagccacaac aagacctccc ggccaagat gtccctggtg	1860
atgcctgcca tggcccccaa tgagaccctg tcaggccgtg gggccccggg ggactatgag	1920
gagatgatgc agatcgagtg tgaggtcatg gacaccaggg tgattcacat caagacctcc	1980
acagtgcccc cctcgctccg aaaacagcca tccccaaccc caggcaatgc cacagggtgc	2040
cccttgccag tctctgcagc cagccaggcc caccaggcct cccaccagcc cctctacctc	2100
aatcatccct aa	2112

<210> 16  
 <211> 703  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> CREBL1

<400> 16

Met Ala Glu Leu Met Leu Leu Ser Glu Ile Ala Asp Pro Thr Arg Phe  
1 5 10 15

Phe Thr Asp Asn Leu Leu Ser Pro Glu Asp Trp Gly Leu Gln Asn Ser  
20 25 30

Thr Leu Tyr Ser Gly Leu Asp Glu Val Ala Glu Glu Gln Thr Gln Leu  
35 40 45

Phe Arg Cys Pro Glu Gln Asp Val Pro Phe Asp Gly Ser Ser Leu Asp  
50 55 60

Val Gly Met Asp Val Ser Pro Ser Glu Pro Pro Trp Glu Leu Leu Pro  
65 70 75 80

Ile Phe Pro Asp Leu Gln Val Lys Ser Glu Pro Ser Ser Pro Cys Ser  
85 90 95

Ser Ser Ser Leu Ser Ser Glu Ser Ser Arg Leu Ser Thr Glu Pro Ser  
100 105 110

Ser Glu Ala Leu Gly Val Gly Glu Val Leu His Val Lys Thr Glu Ser  
115 120 125

Leu Ala Pro Pro Leu Cys Leu Leu Gly Asp Asp Pro Thr Ser Ser Phe  
130 135 140

Glu Thr Val Gln Ile Asn Val Ile Pro Thr Ser Asp Asp Ser Ser Asp  
145 150 155 160

Val Gln Thr Lys Ile Glu Pro Val Ser Pro Cys Ser Ser Val Asn Ser  
165 170 175

Glu Ala Ser Leu Leu Ser Ala Asp Ser Ser Ser Gln Ala Phe Ile Gly  
180 185 190

Glu Glu Val Leu Glu Val Lys Thr Glu Ser Leu Ser Pro Ser Gly Cys  
195 200 205

Leu Leu Trp Asp Val Pro Ala Pro Ser Leu Gly Ala Val Gln Ile Ser  
210 215 220

Met Gly Pro Ser Leu Asp Gly Ser Ser Gly Lys Ala Leu Pro Thr Arg  
225 230 235 240

Lys Pro Pro Leu Gln Pro Lys Pro Val Val Leu Thr Thr Val Pro Met

245						250						255				
Pro	Ser	Arg	Ala 260	Val	Pro	Pro	Ser	Thr 265	Thr	Val	Leu	Leu	Gln 270	Ser	Leu	
Val	Gln	Pro 275	Pro	Pro	Val	Ser	Pro 280	Val	Val	Leu	Ile	Gln 285	Gly	Ala	Ile	
Arg	Val 290	Gln	Pro	Glu	Gly	Pro 295	Ala	Pro	Ser	Leu	Pro 300	Arg	Pro	Glu	Arg	
Lys 305	Ser	Ile	Val	Pro	Ala 310	Pro	Met	Pro	Gly	Asn 315	Ser	Cys	Pro	Pro	Glu 320	
Val	Asp	Ala	Lys	Leu 325	Leu	Lys	Arg	Gln	Gln 330	Arg	Met	Ile	Lys	Asn 335	Arg	
Glu	Ser	Ala	Cys 340	Gln	Ser	Arg	Arg	Lys 345	Lys	Lys	Glu	Tyr	Leu 350	Gln	Gly	
Leu	Glu	Ala 355	Arg	Leu	Gln	Ala	Val 360	Leu	Ala	Asp	Asn	Gln 365	Gln	Leu	Arg	
Arg	Glu 370	Asn	Ala	Ala	Leu	Arg 375	Arg	Arg	Leu	Glu	Ala 380	Leu	Leu	Ala	Glu	
Asn 385	Ser	Glu	Leu	Lys	Leu 390	Gly	Ser	Gly	Asn	Arg 395	Lys	Val	Val	Cys	Ile 400	
Met	Val	Phe	Leu	Leu 405	Phe	Ile	Ala	Phe	Asn 410	Phe	Gly	Pro	Val	Ser 415	Ile	
Ser	Glu	Pro	Pro 420	Ser	Ala	Pro	Ile	Ser 425	Pro	Arg	Met	Asn	Lys 430	Gly	Glu	
Pro	Gln	Pro 435	Arg	Arg	His	Leu	Leu 440	Gly	Phe	Ser	Glu	Gln 445	Glu	Pro	Val	
Gln	Gly 450	Val	Glu	Pro	Leu	Gln 455	Gly	Ser	Ser	Gln	Gly 460	Pro	Lys	Glu	Pro	
Gln 465	Pro	Ser	Pro	Thr	Asp 470	Gln	Pro	Ser	Phe	Ser 475	Asn	Leu	Thr	Ala	Phe 480	
Pro	Gly	Gly	Ala	Lys 485	Glu	Leu	Leu	Leu	Arg 490	Asp	Leu	Asp	Gln	Leu	Phe 495	

Leu Ser Ser Asp Cys Arg His Phe Asn Arg Thr Glu Ser Leu Arg Leu  
500 505 510

Ala Asp Glu Leu Ser Gly Trp Val Gln Arg His Gln Arg Gly Arg Arg  
515 520 525

Lys Ile Pro Gln Arg Ala Gln Glu Arg Gln Lys Ser Gln Pro Arg Lys  
530 535 540

Lys Ser Pro Pro Val Lys Ala Val Pro Ile Gln Pro Pro Gly Pro Pro  
545 550 555 560

Glu Arg Asp Ser Val Gly Gln Leu Gln Leu Tyr Arg His Pro Asp Arg  
565 570 575

Ser Gln Pro Ala Phe Leu Asp Ala Ile Asp Arg Arg Glu Asp Thr Phe  
580 585 590

Tyr Val Val Ser Phe Arg Arg Asp His Leu Leu Leu Pro Ala Ile Ser  
595 600 605

His Asn Lys Thr Ser Arg Pro Lys Met Ser Leu Val Met Pro Ala Met  
610 615 620

Ala Pro Asn Glu Thr Leu Ser Gly Arg Gly Ala Pro Gly Asp Tyr Glu  
625 630 635 640

Glu Met Met Gln Ile Glu Cys Glu Val Met Asp Thr Arg Val Ile His  
645 650 655

Ile Lys Thr Ser Thr Val Pro Pro Ser Leu Arg Lys Gln Pro Ser Pro  
660 665 670

Thr Pro Gly Asn Ala Thr Gly Gly Pro Leu Pro Val Ser Ala Ala Ser  
675 680 685

Gln Ala His Gln Ala Ser His Gln Pro Leu Tyr Leu Asn His Pro  
690 695 700

<210> 17

<211> 2013

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<223> DNA that codes for ATF6

<400> 17

atgggggagc cggctggggg tgccggcacc atggagtcac cttttagccc gggactcttt	60
cacaggctgg atgaagattg ggattctgct ctctttgctg aactcgggta tttcacagac	120
actgatgagc tgcaattgga agcagcaaat gagacgtatg aaaacaattt tgataatctt	180
gattttgatt tggatttgat gccttgggag tcagacattt gggacatcaa caaccaaadc	240
tgtacagtta aagatattaa ggcagaacct cagccacttt ctccagcctc ctcaagttat	300
tcagtctcgt ctccctcggtc agtggactct tattcttcaa ctccagcatgt tcctgaggag	360
ttggatttgt cttctagttc tcagatgtct cccctttcct tatatggtga aaactctaata	420
agtctctctt cagcggagcc actgaaggaa gataagcctg tcaactggtc taggaacaag	480
actgaaaatg gactgactcc aaagaaaaaa attcagggtga attcaaaaacc ttcaattcag	540
cccaagcctt tattgcttcc agcagcacc c aagactcaaa caaactccag tgttccagca	600
aaaaccatca ttattcagac agtaccaacg cttatgccat tggcaaagca gcaaccaatt	660
atcagtttac aacctgcacc cactaaaggc cagacgggtt tgctgtctca gcctactgtg	720
gtacaacttc aagcacctgg agttctgccc tctgctcagc cagtccttgc tgttgctggg	780
ggagtcacac agctccctaa tcacgtggtg aatgtggtac cagccccttc agcgaatagc	840
ccagtgaatg gaaaactttc cgtgactaaa cctgtcctac aaagtaccat gagaaatgtc	900
ggttcagata ttgctgtgct aaggagacag caacgtatga taaaaaatcg agaatccgct	960
tgtcagtctc gcaagaagaa gaaagaatat atgctagggt tagaggcgag attaaaggct	1020
gccctctcag aaaacgagca actgaagaaa gaaaatggaa cactgaagcg gcagctggat	1080
gaagttgtgt cagagaacca gaggtctaaa gtccctagtc caaagcgaag agttgtctgt	1140
gtgatgatag tattggcatt tataatactg aactatggac ctatgagcat gttggaacag	1200
gattccagga gaatgaaccc tagtgtgagc cctgcaaata aaaggaggca ccttctagga	1260
ttttctgcta aagaggcaca ggacacatca gatggtatta tccagaaaaa cagctacaga	1320
tatgatcatt ctgtttcaaa tgacaaagcc ctgatggtgc taactgaaga accattgctt	1380
tacattcctc cacctccttg tcagccccta attaacacaa cagagtctct cagggttaaat	1440
catgaacttc gaggatgggt tcatagacat gaagtagaaa ggaccaagtc aagaagaatg	1500
acaaataatc aacagaaaac ccgtattctt cagggtgctc tggaacaggg ctcaaattct	1560
cagctgatgg ctgttcaata cacagaaacc actagtagta tcagcaggaa ctcaggggagt	1620
gagctacaag tgtattatgc ttcacccaga agttatcaag acttttttga agccatccgc	1680
agaaggggag acacatttta tgttgtgtca tttcgaaggg atcacctgct gttaccagct	1740
accacccata acaagaccac aagacaaaa atgtcaattg tgttaccagc aataaacata	1800
aatgagaatg tgatcaatgg gcaggactac gaagtgatga tgcagattga ctgtcagggtg	1860
atggacacca ggatcctcca tatcaaaagt tcgtcagttc ctcttacct ccgagatcag	1920

cagaggaatc aaaccaacac cttcttttggc tcccctcccg cagccacaga ggcaaccac 1980  
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<210> 18  
 <211> 670  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> ATF6

<400> 18

Met Gly Glu Pro Ala Gly Val Ala Gly Thr Met Glu Ser Pro Phe Ser  
 1 5 10 15

Pro Gly Leu Phe His Arg Leu Asp Glu Asp Trp Asp Ser Ala Leu Phe  
 20 25 30

Ala Glu Leu Gly Tyr Phe Thr Asp Thr Asp Glu Leu Gln Leu Glu Ala  
 35 40 45

Ala Asn Glu Thr Tyr Glu Asn Asn Phe Asp Asn Leu Asp Phe Asp Leu  
 50 55 60

Asp Leu Met Pro Trp Glu Ser Asp Ile Trp Asp Ile Asn Asn Gln Ile  
 65 70 75 80

Cys Thr Val Lys Asp Ile Lys Ala Glu Pro Gln Pro Leu Ser Pro Ala  
 85 90 95

Ser Ser Ser Tyr Ser Val Ser Ser Pro Arg Ser Val Asp Ser Tyr Ser  
 100 105 110

Ser Thr Gln His Val Pro Glu Glu Leu Asp Leu Ser Ser Ser Ser Gln  
 115 120 125

Met Ser Pro Leu Ser Leu Tyr Gly Glu Asn Ser Asn Ser Leu Ser Ser  
 130 135 140

Ala Glu Pro Leu Lys Glu Asp Lys Pro Val Thr Gly Pro Arg Asn Lys  
 145 150 155 160

Thr Glu Asn Gly Leu Thr Pro Lys Lys Lys Ile Gln Val Asn Ser Lys  
 165 170 175

Pro Ser Ile Gln Pro Lys Pro Leu Leu Leu Pro Ala Ala Pro Lys Thr



180						185						190					
Gln	Thr	Asn	Ser	Ser	Val	Pro	Ala	Lys	Thr	Ile	Ile	Ile	Gln	Thr	Val		
		195					200					205					
Pro	Thr	Leu	Met	Pro	Leu	Ala	Lys	Gln	Gln	Pro	Ile	Ile	Ser	Leu	Gln		
	210						215				220						
Pro	Ala	Pro	Thr	Lys	Gly	Gln	Thr	Val	Leu	Leu	Ser	Gln	Pro	Thr	Val		
	225				230					235					240		
Val	Gln	Leu	Gln	Ala	Pro	Gly	Val	Leu	Pro	Ser	Ala	Gln	Pro	Val	Leu		
				245					250					255			
Ala	Val	Ala	Gly	Gly	Val	Thr	Gln	Leu	Pro	Asn	His	Val	Val	Asn	Val		
			260					265					270				
Val	Pro	Ala	Pro	Ser	Ala	Asn	Ser	Pro	Val	Asn	Gly	Lys	Leu	Ser	Val		
		275					280					285					
Thr	Lys	Pro	Val	Leu	Gln	Ser	Thr	Met	Arg	Asn	Val	Gly	Ser	Asp	Ile		
	290						295				300						
Ala	Val	Leu	Arg	Arg	Gln	Gln	Arg	Met	Ile	Lys	Asn	Arg	Glu	Ser	Ala		
	305				310					315					320		
Cys	Gln	Ser	Arg	Lys	Lys	Lys	Lys	Glu	Tyr	Met	Leu	Gly	Leu	Glu	Ala		
				325					330					335			
Arg	Leu	Lys	Ala	Ala	Leu	Ser	Glu	Asn	Glu	Gln	Leu	Lys	Lys	Glu	Asn		
			340					345					350				
Gly	Thr	Leu	Lys	Arg	Gln	Leu	Asp	Glu	Val	Val	Ser	Glu	Asn	Gln	Arg		
		355					360					365					
Leu	Lys	Val	Pro	Ser	Pro	Lys	Arg	Arg	Val	Val	Cys	Val	Met	Ile	Val		
	370						375				380						
Leu	Ala	Phe	Ile	Ile	Leu	Asn	Tyr	Gly	Pro	Met	Ser	Met	Leu	Glu	Gln		
	385				390					395					400		
Asp	Ser	Arg	Arg	Met	Asn	Pro	Ser	Val	Ser	Pro	Ala	Asn	Gln	Arg	Arg		
				405					410					415			
His	Leu	Leu	Gly	Phe	Ser	Ala	Lys	Glu	Ala	Gln	Asp	Thr	Ser	Asp	Gly		
			420					425					430				

Ile	Ile	Gln	Lys	Asn	Ser	Tyr	Arg	Tyr	Asp	His	Ser	Val	Ser	Asn	Asp	435	440	445
Lys	Ala	Leu	Met	Val	Leu	Thr	Glu	Glu	Pro	Leu	Leu	Tyr	Ile	Pro	Pro	450	455	460
Pro	Pro	Cys	Gln	Pro	Leu	Ile	Asn	Thr	Thr	Glu	Ser	Leu	Arg	Leu	Asn	465	470	475
His	Glu	Leu	Arg	Gly	Trp	Val	His	Arg	His	Glu	Val	Glu	Arg	Thr	Lys	485	490	495
Ser	Arg	Arg	Met	Thr	Asn	Asn	Gln	Gln	Lys	Thr	Arg	Ile	Leu	Gln	Gly	500	505	510
Ala	Leu	Glu	Gln	Gly	Ser	Asn	Ser	Gln	Leu	Met	Ala	Val	Gln	Tyr	Thr	515	520	525
Glu	Thr	Thr	Ser	Ser	Ile	Ser	Arg	Asn	Ser	Gly	Ser	Glu	Leu	Gln	Val	530	535	540
Tyr	Tyr	Ala	Ser	Pro	Arg	Ser	Tyr	Gln	Asp	Phe	Phe	Glu	Ala	Ile	Arg	545	550	555
Arg	Arg	Gly	Asp	Thr	Phe	Tyr	Val	Val	Ser	Phe	Arg	Arg	Asp	His	Leu	565	570	575
Leu	Leu	Pro	Ala	Thr	Thr	His	Asn	Lys	Thr	Thr	Arg	Pro	Lys	Met	Ser	580	585	590
Ile	Val	Leu	Pro	Ala	Ile	Asn	Ile	Asn	Glu	Asn	Val	Ile	Asn	Gly	Gln	595	600	605
Asp	Tyr	Glu	Val	Met	Met	Gln	Ile	Asp	Cys	Gln	Val	Met	Asp	Thr	Arg	610	615	620
Ile	Leu	His	Ile	Lys	Ser	Ser	Ser	Val	Pro	Pro	Tyr	Leu	Arg	Asp	Gln	625	630	635
Gln	Arg	Asn	Gln	Thr	Asn	Thr	Phe	Phe	Gly	Ser	Pro	Pro	Ala	Ala	Thr	645	650	655
Glu	Ala	Thr	His	Val	Val	Ser	Thr	Ile	Pro	Glu	Ser	Leu	Gln			660	665	670

<210> 19  
 <211> 36  
 <212> DNA

<213> Artificial  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:3  
 for use as a primer to obtain mature HtrA2 DNA  
 <400> 19  
 catatggccg tccctagccc gccgcccgc tctccc 36  
 <210> 20  
 <211> 35  
 <212> DNA  
 <213> Artificial  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:3  
 for use as a primer to obtain mature HtrA2 DNA  
 <400> 20  
 ctcgagttct gtgacctcag gggtcacata taagg 35  
 <210> 21  
 <211> 40  
 <212> DNA  
 <213> Artificial  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:3  
 for use as a primer to obtain mature HtrA2(S306A) DNA  
 <400> 21  
 gctattgatt ttggaaacgc tggagggtccc ctggttaacc 40  
 <210> 22  
 <211> 40  
 <212> DNA  
 <213> Artificial  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:3  
 for use as a primer to obtain mature HtrA2(S306A) DNA  
 <400> 22  
 ggttaaccag gggacctcca gcgtttccaa aatcaatagc 40  
 <210> 23  
 <211> 27  
 <212> DNA  
 <213> Artificial  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1  
 5 for use as a primer to obtain CREBL1 DNA  
 <400> 23  
 gcgaattcgc catggcggag ctgatgc 27  
 <210> 24

<211> 28  
 <212> DNA  
 <213> Artificial  
  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1  
 5 for use as a primer to obtain CREBL1 DNA  
  
 <400> 24  
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 <210> 25  
 <211> 30  
 <212> DNA  
 <213> Artificial  
  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1  
 5 for use as a primer to obtain CREBL1 DNA  
  
 <400> 25  
 gcggatcccg cgagctgat gctgctcagc 30  
  
 <210> 26  
 <211> 33  
 <212> DNA  
 <213> Artificial  
  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1  
 5 for use as a primer to obtain CREBL1 DNA  
  
 <400> 26  
 cctcgagggt tagggatgat tgaggtagag ggg 33  
  
 <210> 27  
 <211> 30  
 <212> DNA  
 <213> Artificial  
  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1  
 7 for use as a primer to obtain ATF6 DNA  
  
 <400> 27  
 agttccaggg aaaaggaact tgtgaaatgg 30  
  
 <210> 28  
 <211> 30  
 <212> DNA  
 <213> Artificial  
  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1  
 7 for use as a primer to obtain ATF6 DNA  
  
 <400> 28  
 acgctcagtt ttccacatag ctgcgggtgc 30

<210> 29  
 <211> 39  
 <212> DNA  
 <213> Artificial  
  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1  
 7 for use as a primer to obtain ATF6 DNA  
  
 <400> 29  
 aaagatatca tgggggagcc ggctgggggtt gccggcacc 39  
  
 <210> 30  
 <211> 39  
 <212> DNA  
 <213> Artificial  
  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1  
 7 for use as a primer to obtain ATF6 DNA  
  
 <400> 30  
 aaactcgagc tattgtaatg actcagggat ggtgctgac 39  
  
 <210> 31  
 <211> 39  
 <212> DNA  
 <213> Artificial  
  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:1  
 7 for use as a primer to obtain ATF6 DNA  
  
 <400> 31  
 aaaagatcta tgggggagcc ggctgggggtt gccggcacc 39  
  
 <210> 32  
 <211> 36  
 <212> DNA  
 <213> Artificial  
  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:3  
 for use as a primer to obtain mature HtrA2(delta AVPS) DNA  
  
 <400> 32  
 gagctcatgc cgccgcccgc ttctccccgg agtcag 36  
  
 <210> 33  
 <211> 36  
 <212> DNA  
 <213> Artificial  
  
 <220>  
 <223> Designed polynucleotide based on the base sequence of SEQ ID NO:3  
 for use as a primer to obtain mature HtrA2(GVPS) DNA  
  
 <400> 33

gagctcatgg gcgtccctag cccgccgcc gcttct

36

<210> 34

<211> 1398

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<223> DNA that codes for HNF-4alpha

<400> 34

atggacatgg ccgactacag tgctgcactg gaccagcct acaccaccct ggaatttgag	60
aatgtgcagg tgttgacgat gggcaatgac acgtcccat cagaaggcac caacctcaac	120
gcgccaaca gcctgggtgt cagcgccctg tgtgccatct gcggggaccg ggccacgggc	180
aaacactacg gtgcctcgag ctgtgacggc tgcaagggct tcttcggag gagcgtgcgg	240
aagaaccaca tgtactcctg cagatttagc cggcagtgcg tggtagacaa agacaagagg	300
aaccagtgcc gctactgcag gctcaagaaa tgcttcggg ctggcatgaa gaaggaagcc	360
gtccagaatg agcgggaccg gatcagcact cgaagggtcaa gctatgagga cagcagcctg	420
ccctccatca atgcgctcct gcaggcggag gtcctgtccc gacagatcac ctccccgcgc	480
tccgggatca acggcgacat tcgggcgaag aagattgccg gcacgcgaga tgtgtgtgag	540
tccatgaagg agcagctgct ggttctcgtt gagtgggcca agtacatccc agctttctgc	600
gagctcccc tggacgacca ggtggccctg ctgagagccc atgctggcga gcacctgctg	660
ctcggagcca ccaagagatc catggtgttc aaggacgtgc tgctcctagg caatgactac	720
attgtccctc ggcaactgcc ggagctggcg gagatgagcc ggggtgtccat acgcacacct	780
gacgagctgg tgctgccctt ccaggagctg cagatcgatg acaatgagta tgacctctc	840
aaagccatca tcttctttga cccagatgcc aaggggctga gcgatccagg gaagatcaag	900
cggctgcgtt cccagggtgca ggtgagcttg gaggactaca tcaacgaccg ccagtatgac	960
tcgctgggcc gctttggaga gctgctgctg ctgctgcca ccttgacagag catcacctgg	1020
cagatgatcg agcagatcca gttcatcaag ctcttcggca tggccaagat tgacaacctg	1080
ttgcaggaga tgctgctggg aggggtcccc agcagatgcac cccatgcca cccccctg	1140
cacctcacc tgatgcagga acatatggga accaacgtca tcgttgccaa cacaatgccc	1200
actcacctca gcaacggaca gatgtgtgag tggccccgac ccaggggaca ggcagccacc	1260
cctgagaccc cacagccctc accgccaggt ggctcagggt ctgagcccta taagctcctg	1320
ccgggagccg tcgccacaat cgtcaagccc ctctctgcca tccccagcc gaccatcacc	1380
aagcaggaag ttatctag	1398

<210> 35  
<211> 465  
<212> PRT  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<223> HNF-4alpha

<400> 35

Met Asp Met Ala Asp Tyr Ser Ala Ala Leu Asp Pro Ala Tyr Thr Thr  
1 5 10 15

Leu Glu Phe Glu Asn Val Gln Val Leu Thr Met Gly Asn Asp Thr Ser  
20 25 30

Pro Ser Glu Gly Thr Asn Leu Asn Ala Pro Asn Ser Leu Gly Val Ser  
35 40 45

Ala Leu Cys Ala Ile Cys Gly Asp Arg Ala Thr Gly Lys His Tyr Gly  
50 55 60

Ala Ser Ser Cys Asp Gly Cys Lys Gly Phe Phe Arg Arg Ser Val Arg  
65 70 75 80

Lys Asn His Met Tyr Ser Cys Arg Phe Ser Arg Gln Cys Val Val Asp  
85 90 95

Lys Asp Lys Arg Asn Gln Cys Arg Tyr Cys Arg Leu Lys Lys Cys Phe  
100 105 110

Arg Ala Gly Met Lys Lys Glu Ala Val Gln Asn Glu Arg Asp Arg Ile  
115 120 125

Ser Thr Arg Arg Ser Ser Tyr Glu Asp Ser Ser Leu Pro Ser Ile Asn  
130 135 140

Ala Leu Leu Gln Ala Glu Val Leu Ser Arg Gln Ile Thr Ser Pro Val  
145 150 155 160

Ser Gly Ile Asn Gly Asp Ile Arg Ala Lys Lys Ile Ala Ser Ile Ala  
165 170 175

Asp Val Cys Glu Ser Met Lys Glu Gln Leu Leu Val Leu Val Glu Trp  
180 185 190

Ala Lys Tyr Ile Pro Ala Phe Cys Glu Leu Pro Leu Asp Asp Gln Val  
195 200 205

Ala Leu Leu Arg Ala His Ala Gly Glu His Leu Leu Leu Gly Ala Thr  
 210 215 220

Lys Arg Ser Met Val Phe Lys Asp Val Leu Leu Leu Gly Asn Asp Tyr  
 225 230 235 240

Ile Val Pro Arg His Cys Pro Glu Leu Ala Glu Met Ser Arg Val Ser  
 245 250 255

Ile Arg Ile Leu Asp Glu Leu Val Leu Pro Phe Gln Glu Leu Gln Ile  
 260 265 270

Asp Asp Asn Glu Tyr Ala Tyr Leu Lys Ala Ile Ile Phe Phe Asp Pro  
 275 280 285

Asp Ala Lys Gly Leu Ser Asp Pro Gly Lys Ile Lys Arg Leu Arg Ser  
 290 295 300

Gln Val Gln Val Ser Leu Glu Asp Tyr Ile Asn Asp Arg Gln Tyr Asp  
 305 310 315 320

Ser Arg Gly Arg Phe Gly Glu Leu Leu Leu Leu Leu Pro Thr Leu Gln  
 325 330 335

Ser Ile Thr Trp Gln Met Ile Glu Gln Ile Gln Phe Ile Lys Leu Phe  
 340 345 350

Gly Met Ala Lys Ile Asp Asn Leu Leu Gln Glu Met Leu Leu Gly Gly  
 355 360 365

Ser Pro Ser Asp Ala Pro His Ala His His Pro Leu His Pro His Leu  
 370 375 380

Met Gln Glu His Met Gly Thr Asn Val Ile Val Ala Asn Thr Met Pro  
 385 390 395 400

Thr His Leu Ser Asn Gly Gln Met Cys Glu Trp Pro Arg Pro Arg Gly  
 405 410 415

Gln Ala Ala Thr Pro Glu Thr Pro Gln Pro Ser Pro Pro Gly Gly Ser  
 420 425 430

Gly Ser Glu Pro Tyr Lys Leu Leu Pro Gly Ala Val Ala Thr Ile Val  
 435 440 445

Lys Pro Leu Ser Ala Ile Pro Gln Pro Thr Ile Thr Lys Gln Glu Val  
 450 455 460



Ile  
465